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Improved Process for the Preparation of Halo Substituted Mannich Bases of Substituted Benzimidazoles

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Abstract: ***Mannich bases are the end products of mannich reaction and are known as beta amino ketone carrying compounds. Mannich reaction is a carbon carbon bond forming nucleophilic addition reaction which helps in synthesizing N-methyl derivatives and many other drug molecules. Mannich base derivatives of benzimidazoles possess many pharmacological properties such as anti-oxidant, anti-inflammatory, anticancer, antiviral, anthelmintic and play an important role in medical field. As these drugs are clinically useful in treatment of microbial infections and exhibit other therapeutic activities also, so this encouraged the development of more potent, novel and clinically significant compounds.***

Keywords: Benzimidazoles, Antimicrobial activity, Anti-fungal activity, mannich base, secondary amine

1. Introduction

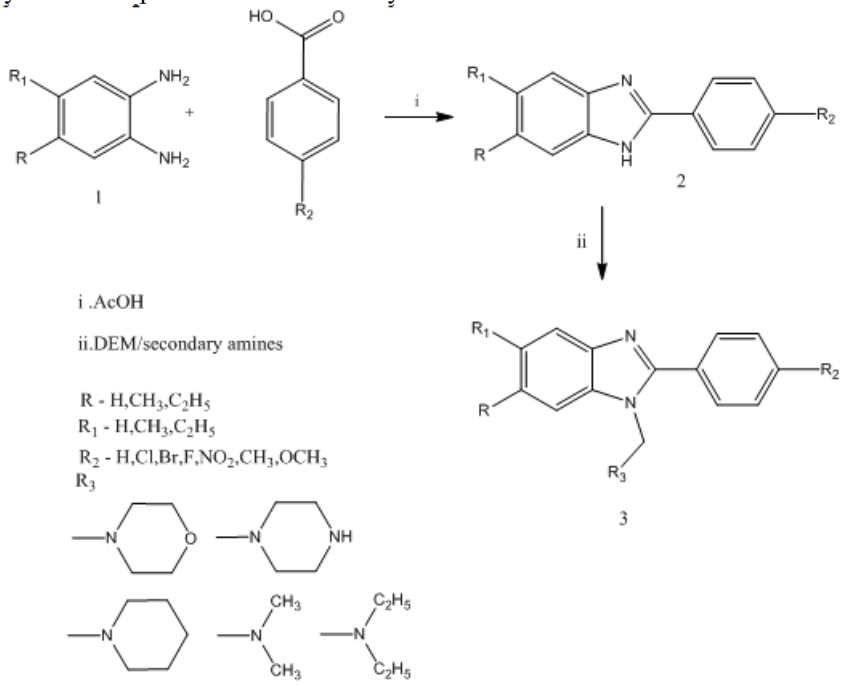
The aminoalkylation of aromatic substrates by the Mannich reaction is of considerable importance for the synthesis and modification of biologically active compounds[1, 2]. It also provides a convenient access to many useful synthetic building blocks because the amino group can be easily converted into a variety of other functionalities[3,4]. Antimicrobial drugs or chemicals are the substances used to kill or slow down the growth of microorganisms. They include antibiotics, antiviral, antifungal and anti-parasitic agents.[3] Antimicrobial chemotherapy has been used from last six decades against infectious diseases caused by a variety of pathogens. Since then, many antimicrobial drugs were discovered, hundreds of drugs using now a days. Anti-microbial drugs are most commonly available today.[4] Since the introduction of penicillin as antibiotics in the control of infectious diseases, frequent use of antimicrobial drugs cause a variety of problems, such as drug resistance, allergic reactions, nutritional loss, toxicity and much more. Almost all of the major categories of antibiotics in the clinical application showed resistance to microorganism specially β- lactam, macrolides, vancomycin and quinolones derived bacterial drug's resistance is a source of concern for healthcare officials. The effective treatment against microbial agents is limiting day by day.[5,6] Many other antimicrobial drugs are toxic too. So, there is a real need to discover new compounds with high efficiency towards pathogens and less toxicity, which may be different from available resistant drugs. This provides a great opportunity to synthetic chemists for the synthesis of such new compounds having lower cytotoxicity and better antimicrobial properties. The biological activity of the compounds depends on structure of molecule.[7] It has been shown that heterocyclic compounds are more biological active as compared to others.[8] Heterocyclic compounds particularly five and six member heterocycles have attracted the attention of pharmaceutical community over the years due to their therapeutic value.[9] Polyfunctionalized heterocyclic compounds containing Nitrogen, sulphur, oxygen as heteroatoms play important roles in the drug discovery process.[10] Benzimidazole is one such compound which attract attention of synthetic chemists for the synthesis of antimicrobial drugs.[11] The benzimidazoles contain a phenyl ring fused with imidazole ring.[12] This compound has various applications in a number of fields. Benzimidazole contain nucleus plays an important role in various medicines.[13] The role of purines in biological systems is well known and it was discovered that 5, 6-dimethyl-1-(α-Dribofuranosyl)benzimidazole is an important part of Vitamin B 12 structure, which leads a massive research on benzimidazoles especially for the synthesizing new such compounds having biological applications. This stimulated great interest in the structural study of Benzimidazole and related compounds and much success was made in pharmaceutical industry. Some commercially used Benzimidazole based drugs are; azomycin, metronidazole, thiabendazole, benomyl, clemizole, enviroxime, irtemazole, astemizole, omeprazole, pentoprazole, thiabendazole and nocodazole.[14] Benzimidazole undergoes different reactions i.e. electrophilic and nucleophilic addition, electrocyclic reactions and thermal oxidation

In this research the synthesis of mannich bases of benzimidazoles are prepared by using diethoxy methane or dimethoxy methane instead of formaldehyde which used in literature. The active methylene group present in diethoxymethane moiety abstract lone pair of electrons from nitrogen atom of imidazole, as methoxy or ethoxy groups are easily removable groups hence when it attacs secondary amine ethanol or methanol formed as byproduct.

2. Experimental

The following experimental methods were used for the characterization of the synthesized compounds. The melting points (m.p.) were determined using Gallenkamp melting point apparatus. The IR spectra were recorded in KBr discs on a Perkin Elmer 1000 FT-IR spectrophotometer (υmax in cm-). The 1H NMR and 13C NMR spectra were collected in DMSO-d6 or ($CDCl_3$) using 400 M Hz . The chemical shifts

were reported as parts per million (d ppm) and the coupling constants (J) are given in Hz, tetra methyl silane (TMS) was used as an internal standard. The mass spectra (m/z, %) were obtained on electron impact using an AEI MS902 mass spectrometer. The purity of all compounds was checked by TLC using glass plates coated with silica gel and dichloromethane/methanol (9:1) as a solvent system. Spectral data (IR, NMR, and mass spectra) confirmed the structures of the synthesized compounds.

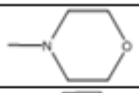
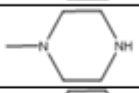
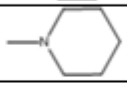
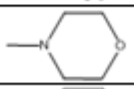
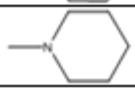


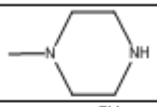
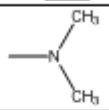
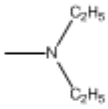
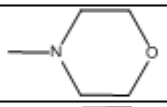
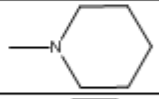
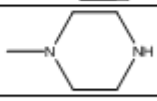
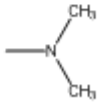
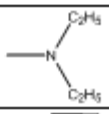
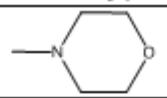
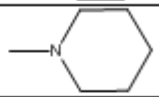
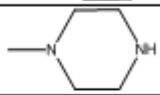
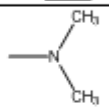
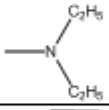
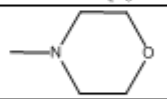
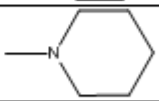
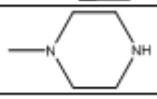
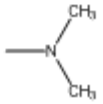
SCHEME - I

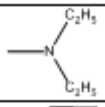
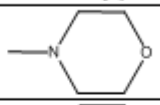
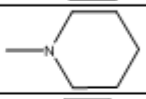
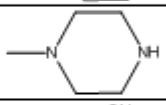
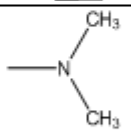
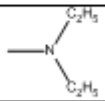
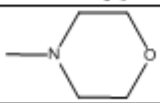
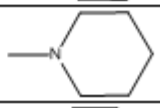
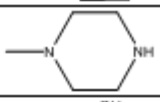
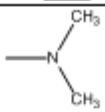
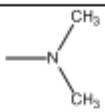
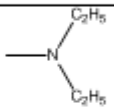
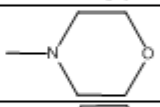
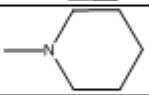
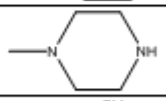
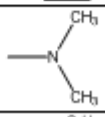
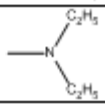
General procedure for the preparation of benzimidazoles (2a-2h):A solution of benzoic acid (0.01 moles) and substitute phenyl diamine (0.01 moles) in 20 ml acetic acid was refluxed for 3-4 hours, after reaction completion, the precipitate obtained after cooling was Recrystalize from methanol.

General procedure for the synthesis of mannich bases (1): Mannich base were prepared by a solution of substituted benzimidazoles (0.005 moles) in 10 ml ethanol, 0.005 moles secondary amine and 0.05 moles diethoxy methane of dimethoxy methane and then the reaction mixture was refluxed for 8 hours, on cooling, the product formed was filtered, dried and re-crystallized from dimethyl formamide ,specific details given to each compound.

Table 1: Physico chemical analysis

S.No	Compounds	M.W	R	R_1	R2	R_3	m.p(°C)	yield
2aa	$C_{18}H_2N_3O$	293.36	H	H	H		241-243	85
2ab	$C_{18}H_{20}N_4$	292.3	H	H	H		234-235	78
2ac	$C_{19}H_{21}N_3$	291.3	H	H	H		243-245	85
2ad	$C_{16}H_{17}N_3$	251.3	H	H	H		235-237	89
2ae	$C_{18}H_{21}N_3$	279.3	H	H	H		241-243	93
5ba	$C_{18}H_{18}ClN_3O$	327.8	H	H	Cl		236-238	92
2bb	$C_{19}H_{20}ClN_3$	325.8	H	H	Cl		245-246	89

S.No	Compounds	M.W	R	R_1	R2	R_3	m.p(°C)	yield
2bc	$C_{18}H_{19}ClN_4$	326.8	H	H	Cl		234-235	94
2bd	$C_{16}H_{16}ClN_3$	285.7	H	H	Cl		214-215	92
2be	$C_{18}H_{20}ClN_3$	313.8	H	H	Cl		240-241	94
2ca	$C_{20}H_{22}ClN_3O$	355.8	CH3	CH3	Cl		223-224	87
2cb	$C_{21}H_{24}ClN_3$	353.8	CH3	CH3	Cl		235-236	85
2cc	$C_{20}H_{23}ClN_4$	354.8	CH3	CH3	Cl		241-242	87
2cd	$C_{18}H_{20}ClN_3$	313.8	CH3	CH3	Cl		238-239	88
2ce	$C_{20}H_{24}ClN_3$	341.8	CH3	CH3	Cl		218-219	85
2da	$C_{22}H_{26}ClN_3O$	389.9	C_2H_5	C_2H_5	Cl		223-224	84
2db	$C_{23}H_{28}ClN_3$	381.9	C_2H_5	C_2H_5	Cl		221-222	83
2dc	$C_{22}H_{27}ClN_4$	382.9	C_2H_5	C_2H_5	Cl		235-236	82
2dd	$C_{20}H_{24}ClN_3$	341.8	C_2H_5	C_2H_5	Cl		228-229	85
2de	$C_{22}H_{28}ClN_3$	369.9	C_2H_5	C_2H_5	Cl		235-236	87
2ea	$C_{22}H_{26}BrN_3O$	428.3	C_2H_5	C_2H_5	Br		235-236	85
2eb	$C_{23}H_{28}BrN_3$	426.4	C_2H_5	C_2H_5	Br		246-247	89
2ec	$C_{22}H_{27}BrN_4$	427.38	C_2H_5	C_2H_5	Br		235-236	85
2ed	$C_{20}H_{24}BrN_3$	386.3	C_2H_5	C_2H_5	Br		223-224	84

S.No	Compounds	M.W	R	R_1	R2	R_3	m.p(°C)	yield
2ee	$C_{22}H_{28}BrN_3$	414.38	C_2H_5	C_2H_5	Br		236-237	85
2fa	$C_{20}H_{22}BrN_3O$	400.3	CH3	CH3	Br		228-230	87
2fb	$C_{21}H_{24}BrN_3$	398.3	CH3	CH3	Br		218-220	86
2fc	$C_{20}H_{23}BrN_4$	399.3	CH3	CH3	Br		198-200	79
2fd	$C_{18}H_{20}BrN_3$	358.2	CH3	CH3	Br		176-179	68
2fe	$C_{20}H_{24}BrN_3$	386.32	CH3	CH3	Br		168-170	59
2ga	$C_{18}H_{18}BrN_3O$	372.2	H	H	Br		178-201	62
2gb	$C_{19}H_{20}BrN_3$	370.2	H	H	Br		172-175	64
2gc	$C_{18}H_{19}BrN_4$	371.2	H	H	Br		176-178	74
2gd	$C_{16}H_{16}BrN_3$	330.2	H	H	Br		168-170	69
2gd	$C_{16}H_{16}BrN_3$	330.2	H	H	Br		168-170	69
2ge	$C_{18}H_{20}BrN_3$	358.2	H	H	Br		172-174	59
2ha	$C_{18}H_{18}FN_3O$	311.3	H	H	F		165-167	72
2hb	$C_{19}H_{20}FN_3$	309.3	H	H	F		167-169	71
2hc	$C_{18}H_{19}FN_4$	310.3	H	H	F		158-160	68
2hd	$C_{16}H_{16}FN_3$	269.3	H	H	F		162-164	67
2he	$C_{18}H_{20}FN_3$	297.3	H	H	F		158-160	64

Preparation of 2-(4-fluoroPhenyl)benzimidazole (A): Phenyldiamine (10 g, 0.092 moles) and 4-fluorobenzoic acid (12.9 g, 0.092 moles) in Acetic acid (50 ml) are refluxed for 5 hours, after reaction completion, the reaction mass was cooled and the obtained precipitate is filtered and Recrystalize from methanol and dried to get title compound (16.8 g, 88%)mp 196°C, ((δH ($CDCl_3$) 13.30 (1H, NH), 8.29 (2H,=C-H), 7.58 (2H, =C-H)) 7.45 (2H, F-C=H); 7.23 (2H, =C-H) 7.2 (2H),δC ($CDCl_3$) 151.2 (C=N), 139.14, 136.4,135.1, 132.2, 129.2,128.4, 122.1 and 115.2, MS (EI): m/z 212. [M+]

Preparation of 2-(4-chloroPhenyl)benzimidazole (B): Phenyldiamine (10 g, 0.092 moles) and 4-chlorobenzoic acid (14.4 g, 0.092 moles) in Acetic acid (50 ml) are refluxed for 5 hours, after reaction completion, the reaction mass was cooled and the obtained precipitate is filtered and Recrystalize from methanol and dried to get title compound (16.8 g, 88%)mp 201°C, ((δH ($CDCl_3$) 13.30 (1H, NH), 8.19 (2H,=C-H), 7.59 (2H, =C-H)) 7.49 (2H, Cl-C=H); 7.23 (2H, =C-H),δC ($CDCl_3$) 151.2 (C=N), 139.14, 136.4,135.6,132.1,131.2, 130.2,128.4, 122.1 and 115.4 MS (EI): m/z 228[M+]

Preparation of 2-(4-bromoPhenyl)benzimidazole (C): Phenyldiamine (10 g, 0.092 moles) and 4-bromobenzoic acid (18.6 g, 0.092 moles) in Acetic acid (50 ml) are refluxed for 5 hours, after reaction completion, the reaction mass was cooled and the obtained precipitate is filtered and Recrystalize from methanol and dried to get title compound (21.4g, 85%)mp 221°C, ((δH ($CDCl_3$) 13.30 (1H, NH), 8.19 (2H,=C-H), 7.59 (2H, =C-H)) 7.49 (2H, Br-C=H); 7.23 (2H, =C-H),δC($CDCl_3$) 151.2 (C=N), 139.14, 136.4,135.6,132.1,131.2, 130.2,128.4, 122.1 and 115.4 MS (EI): m/z 273[M+]

Preparation of substituted2-(4-nitrophenyl) benzimidazoles (D): Phenyldiamine (10 g, 0.092 moles) and 4-nitrobenzoic acid (15.6 g, 0.092 moles) in Acetic acid (50 ml) are refluxed for 5 hours, after reaction completion, the reaction mass was cooled and the obtained precipitate is filtered and Recrystalize from methanol and dried to get title compound (18.4 g, 85%) mp 201°C, ((δH ($CDCl_3$) 13.30 (1H, NH), 8.52 (2H,=C-H), 8.49 (2H, =C-H)) 7.59 (2H, C=H); 7.23 (2H, =C-H),δC ($CDCl_3$) 151.24(C=N), 147.5 (-C-NO2),139.14, 136.4,126.4, 123.1, 122.5 and 115.2.; υmax /cm-1 (KBr) 3432 (N-H), 3049 (C-H, sp2), MS (EI): m/z 239[M+]

3. Preparation of Mannich base from 2-(4-halophenyl) benzimidazoles using dimethoxy methane/diethoxy methane

2-(4-fluorophenyl)-1-[(morpholin-4-yl)methyl]-1H-benzimidazole(2aa): light brown color solid, 2-(4-fluorophenyl)benzimidazole (0.005 moles), morpholine(0.42 g,0.005 moles) and diethoxymethane (0.005 moles) are refluxed in ethanol for 4 hours, after reaction completion, the reaction mass is cooled to ambient temperature, the obtained solid was filtered, recrystallized from Dimethyl formamide and dried to get title compound (1.24 g, 85%)mp 192°C, ((δH ($CDCl_3$) 7.88 (2H,=CH), 7.69 (2H) 7.30 (1H), 7.18(1H) 7.17 (2H),7.14 (1H), 6.61 (1H),4.82 (2H,N-CH2-N) 3.66 (4H, O-CH2) and 2.55 (4H,--CH2) ,δC ($CDCl_3$) 163.1 (=C-F), 137.1 (=C-N), 135.14 (=C-N), 130.1(=C), 131.2, 130.7, 130.2,128.4, 121.8, 119.8,118.7,115.2, 109.2, 66.3(-C-O), 60.9 (N-C-N) and 51.8 (C-N).; υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 311.3 (M+1.)

2-(4-fluorophenyl)-1-[(piperidin-1-yl)methyl]-1H-benzimidazole(2ab): yellow color solid δH ($CDCl_3$) 7.88 (2H,=CH), 7.69 (2H) 7.30 (1H), 7.18(1H) 7.17 (2H),7.14 (1H), 6.61 (1H),4.82 (2H,N-CH2-N), 2.55 (4H,--CH2),1.65 (4H) AND 1.01 (2H) ,δC ($CDCl_3$) 163.1 (=C-F), 137.1 (=C-N), 135.14 (=C-N), 130.1(=C), 131.2, 130.7, 130.2,128.4, 121.8, 119.8,118.7,115.2, 109.2, 60.9 (N-C-N),51.8 (C-N), 22.4 and 14.2.; υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 309 (M+1.)

2-(4-fluorophenyl)-1-[(piperazin-1-yl)methyl]-1H-benzimidazole(2ac): Brown color solidδH ($CDCl_3$) 7.69 (3H,=CH), 7.35 (1H) 7.28 (1H), 7.20 (2H),7.17(1H) 4.99 (2H,N-CH2-N) 2.79 (4H, NH-CH2) and 2.52 (4H,N-CH2) ,δC ($CDCl_3$) 163.8 (=C-F), 153.1 (=C-N), 142.8 (=C-N),134.4 (=C-N), 130.1(=C), 131.2, 127.02, 123.9, 123.5, 120.0, 116.9,108.6, 60.9 (N-C-N) and 51.8 (C-N).;υmax /cm-1 (KBr) 3342 (N-H), 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 310.2[M+]

1-[2-(4-fluorophenyl)-1H-benzimidazol-1-yl]-N,N-dimethylmethanamine(2ad): Brown color solid,δH ($CDCl_3$) 7.88 (2H,=CH), 7.69 (2H) 7.30 (1H), 7.18(1H) 7.17 (2H),7.14 (1H), 6.61 (1H),4.82 (2H,N-CH2-N) 2.43 (6H, N-CH3) δC ($CDCl_3$) 163.1 (=C-F), 137.1 (=C-N), 135.14 (=C-N), 130.1(=C), 131.2, 130.7, 130.2,128.4, 121.8, 119.8,118.7,115.2, 109.2, 60.9 (N-C-N) and 51.8 (C-N).; υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 269[M+]

N-ethyl-N-{[2-(4-fluorophenyl)-1H-benzimidazol-1-yl]methyl}ethanamine (2ae): off white solid,δH ($CDCl_3$) 7.88 (2H,=CH), 7.69 (2H) 7.30 (1H), 7.18(1H) 7.17 (2H),7.14 (1H), 6.61 (1H),4.82 (2H,N-CH2-N) 2.43 (4H, N-CH3) and 1.02 (6H) δC ($CDCl_3$) 163.1 (=C-F), 137.1 (=C-N), 135.14 (=C-N), 130.1(=C), 131.2, 130.7, 130.2,128.4, 121.8, 119.8,118.7,115.2, 109.2, 60.9 (N-C-N) ,51.8 (C-N) and 14.8.; υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 297[M+]

2-(4-fluorophenyl)-5,6-dimethyl-1-[(morpholin-4-yl)methyl]-1H-benzimidazole (2ba) Off white solid, δH ($CDCl_3$) 7.69 (2H,=CH), 7.48 (1H) 7.20 (2H), 7.02(1H),4.99 (2H,N-CH2-N), 3.66 (4H, O-CH2),2.55(4H, N-CH2), 2.32 (-CH3) and 2.26 (CH3), δC ($CDCl_3$) 163.1 (=C-F), 137.1 (=C-N), 135.14 (=C-N), 130.1(=C), 131.2, 130.7, 130.2,128.4, 121.8, 119.8,118.7,115.2, 109.2, 60.9 (N-C-N) ,51.8 (C-N) and 14.8.; υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 339.4[M+]

2-(4-fluorophenyl)-5,6-dimethyl-1-[(piperidin-1-yl)methyl]-1H-benzimidazole(2bb): Light yellow solid,δH ($CDCl_3$) 7.88 (2H,=CH), 7.69 (2H) 7.30 (1H), 7.18(1H) 7.17 (2H),7.14 (1H), 6.61 (1H),4.82 (2H,N-CH2-N), 2.55 (4H,--

CH2),1.65 (4H) and 1.01 (2H) , IRυmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 326 (M+1.)

2-(4-fluorophenyl)-5,6-dimethyl-1-[(piperazin-1-yl)methyl]-1H-benzimidazole(2bc): Dark brown color solid δH ($CDCl_3$) 7.69 (m, 3H), 7.49 (m, 2H) 7.35 (d, 1H), 7.28 (m,1H),7.17(d,1H) 4.99 (2H,N-CH2-N) 2.79 (4H, NH-CH2) and 2.52 (4H,N-CH2 IR: υmax /cm-1 (KBr) 3342 (N-H), 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 327.2 (M+1)

1-[2-(4-fluorophenyl)-5,6-dimethyl-1H-benzimidazol-1-yl]-N,N-dimethylmethanamine(2bd). Yellow color solid, δH ($CDCl_3$) 7.88 (2H,=CH), 7.69 (2H) 7.28 (1H), 7.18(1H) 7.17 (2H),7.14 (1H), 6.61 (1H),4.82 (2H,N-CH2-N) 2.43 (6H, N-CH3) IR: υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 285.9[M+]

N-{[2-(4-fluorophenyl)-5,6-dimethyl-1H-benzimidazol-1-yl]methyl}-N-ethylethanamine(2be): off white solid, δH ($CDCl_3$) 7.69 (2H,=CH), 7.67 (2H) 7.28 (1H), 7.18(1H) 7.17 (2H),7.14 (1H), 6.61 (1H),4.82 (2H,N-CH2-N) 2.43 (4H, N-CH3) and 1.02 (6H) δC ($CDCl_3$) 163.1 (=C-F), 137.1 (=C-N), 135.14 (=C-N), 130.1(=C), 131.2, 130.7, 130.2,128.4, 121.8, 119.8,118.7,115.2, 109.2, 60.9 (N-C-N) ,51.8 (C-N) and 14.8.; υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 314.2[M+1]

2-(4-chlorophenyl)-5,6-dimethyl-1-[(morpholin-4-yl)methyl]-1H-benzimidazole (2ca). light brown color solid, δH ($CDCl_3$) 7.64 (m, 2H,=CH), 7.49 (m, 2H), 7.48 (d, 2H), 7.02 (s, 1H), 4.99 (2H,N-CH2-N), 3.66 (4H , O-CH2),2.55(4H, N-CH2), 2.32 (-CH3) and 2.26 (CH3), IR.; υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 356.23[M+1]

2-(4-chlorophenyl)-5,6-dimethyl-1-[(piperidin-4-yl)methyl]-1H-benzimidazole (2cb): Light yellow solid, δH ($CDCl_3$) 7.64 (2H,=CH), 7.48 (1H) 7.20 (2H), 7.02(1H),4.99 (2H,N-CH2-N), 2.45(4H, N-CH2), 2.32 (-CH3), 2.26 (CH3), 1.55 (m, 4H) and 1.42 (m, 2H) : IR υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 353.8[M+]

2-(4-chlorophenyl)-5,6-dimethyl-1-[(piperazin-4-yl)methyl]-1H-benzimidazole (2cc): Yellow solid,δH ($CDCl_3$) 7.69 (2H,=CH), 7.48 (1H) 7.20 (2H), 7.02(1H),4.99 (2H,N-CH2-N), 2.72 (m, 4H , N-CH2),2.55(m, 4H, N-CH2), 2.32 (-CH3) and 2.26 (CH3): IR υmax /cm-1 (KBr) 3426, 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 355.2[M+]

1-[2-(4-chlorophenyl)-5,6-dimethyl-1H-benzimidazol-1-yl]-N,N-dimethylmethanamine (2cd): off white solid, δH ($CDCl_3$) 7.64 (m, 2H,=CH), 7.49 (m, 2H) 7.48 (s, 1H), 7.02(s, 1H),4.99 (s, 2H,N-CH2-N),2.32(m, 6H, N-CH3), 2.30 (s, 3H) and 2.26 (s, 3H) IR υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 314.9[M+]

N-{[2-(4-chlorophenyl)-5,6-dimethyl-1H-benzimidazol-1-yl]methyl}-N-ethylethanamine (2ce) off white solid, δH ($CDCl_3$) 7.64 (m, 2H,=CH), 7.49 (m, 2H) 7.48 (s, 1H), 7.02(s, 1H),4.99 (s, 2H,N-CH2-N),2.32(m, 6H, N-CH3), 2.30 (s, 3H), 2.26 (s, 3H) and 1.14 (m, 6H) IR υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 314.9[M+]

2-(4-chlorophenyl)-5,6-diethyl-1-[(morpholin-4-yl)methyl]-1H-benzimidazole (2da). light brown color solid, δH ($CDCl_3$) 7.64 (m, 2H,=CH), 7.49 (m, 2H), 7.48 (d, 2H), 7.02 (s, 1H), 4.99 (2H,N-CH2-N), 3.66 (4H , O-CH2),2.55(4H, N-CH2), 2.63 (m, 4H) and 1.23 (M, 6H), IR.; υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 390.4[M+1]

2-(4-chlorophenyl)-5,6-diethyl-1-[(piperidin-4-yl)methyl]-1H-benzimidazole (2db): Light yellow solid, δH ($CDCl_3$) 7.64 (2H,=CH), 7.48 (1H) 7.20 (2H), 7.02(1H),4.99 (2H,N-CH2-N), 2.45(4H, N-CH2), 2.63 (m, 4H) 1.23 (M, 6H), 1.55 (m, 4H) and 1.42 (m, 2H) : IR υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 382.1[M+]

2-(4-chlorophenyl)-5,6-diethyl-1-[(piperazin-4-yl)methyl]-1H-benzimidazole (2dc): Yellow solid,δH ($CDCl_3$) 7.69 (2H,=CH), 7.48 (1H) 7.20 (2H), 7.02(1H),4.99 (2H,N-CH2-N), 2.72 (m, 4H , N-CH2),2.55(m, 4H, N-CH2), 2.63 (m, 4H) and 1.23 (M, 6H), IR υmax /cm-1 (KBr) 3426, 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 383.2[M+]

1-[2-(4-chlorophenyl)-5,6-diethyl-1H-benzimidazol-1-yl]-N,N-dimethylmethanamine (2dd): off white solid, δH ($CDCl_3$) 7.64 (m, 2H,=CH), 7.49 (m, 2H) 7.48 (s, 1H), 7.02(s, 1H),4.99 (s, 2H,N-CH2-N),2.32(m, 6H, N-CH3), 2.30 (s, 3H) and 2.26 (s, 3H) IR υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 342.1[M+]

N-{[2-(4-chlorophenyl)-5,6-diethyl-1H-benzimidazol-1-yl]methyl}-N-ethylethanamine (2de) off white solid, δH ($CDCl_3$) 7.64 (m, 2H,=CH), 7.49 (m, 2H) 7.48 (s, 1H), 7.02(s, 1H),4.99 (s, 2H,N-CH2-N),2.32(m, 6H, N-CH3), 2.30 (s, 3H), 2.26 (s, 3H) and 1.14 (m, 6H) IR υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 370.1[M+]

2-(4-bromophenyl)-5,6-diethyl-1-[(morpholin-4-yl)methyl]-1H-benzimidazole (2ea). light brown color solid, δH ($CDCl_3$) 7.64 (m, 2H,=CH), 7.49 (m, 2H), 7.48 (d, 2H), 7.02 (s, 1H), 4.99 (2H,N-CH2-N), 3.66 (4H , O-CH2),2.55(4H, N-CH2), 2.63 (m, 4H) and 1.23 (M, 6H), IR.; υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 429.4[M+2]

2-(4-bromophenyl)-5,6-diethyl-1-[(piperidin-4-yl)methyl]-1H-benzimidazole (2eb): Light yellow solid, δH ($CDCl_3$) 7.64 (2H,=CH), 7.48 (1H) 7.20 (2H), 7.02(1H),4.99 (2H,N-CH2-N), 2.45(4H, N-CH2), 2.63 (m, 4H) 1.23 (M, 6H), 1.55 (m, 4H) and 1.42 (m, 2H) : IR υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 326.8[M+]

2-(4-bromophenyl)-5,6-diethyl-1-[(piperazin-4-yl)methyl]-1H-benzimidazole (2ec): Yellow solid,δH ($CDCl_3$) 7.69 (2H,=CH), 7.48 (1H) 7.20 (2H), 7.02(1H),4.99 (2H,N-CH2-N), 2.72 (m, 4H , N-CH2),2.55(m, 4H, N-CH2), 2.63 (m, 4H) and 1.23 (M, 6H), IR υmax /cm-1 (KBr) 3426, 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 427.6[M+]

1-[2-(4-bromophenyl)-5,6-diethyl-1H-benzimidazol-1-yl]-N,N-dimethylmethanamine (2ed): off white solid, δH ($CDCl_3$) 7.64 (m, 2H,=CH), 7.49 (m, 2H) 7.48 (s, 1H), 7.02(s, 1H),4.99 (s, 2H,N-CH2-N),2.32(m, 6H, N-CH3), 2.30 (s, 3H) and 2.26 (s, 3H) IR υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 386.6[M+]

N-{[2-(4-bromophenyl)-5,6-diethyl-1H-benzimidazol-1-yl]methyl}-N-ethylethanamine (2ee) off white solid, δH ($CDCl_3$) 7.64 (m, 2H,=CH), 7.49 (m, 2H) 7.48 (s, 1H), 7.02(s, 1H),4.99 (s, 2H,N-CH2-N),2.32(m, 6H, N-CH3), 2.30 (s, 3H), 2.26 (s, 3H) and 1.14 (m, 6H) IR υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 414.6[M+]

2-(4-bromophenyl)-5,6-dimethyl-1-[(morpholin-4-yl)methyl]-1H-benzimidazole (2fa). light brown color solid, δH ($CDCl_3$) 7.64 (m, 2H,=CH), 7.49 (m, 2H), 7.48 (d, 2H), 7.02 (s, 1H), 4.99 (2H,N-CH2-N), 3.66 (4H , O-CH2),2.55(4H, N-CH2), 2.32 (-CH3) and 2.26 (CH3), IR.; υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 400.6[M+1]

2-(4-bromophenyl)-5,6-dimethyl-1-[(piperidin-4-yl)methyl]-1H-benzimidazole (2fb): Light yellow solid, δH ($CDCl_3$) 7.64 (2H,=CH), 7.48 (1H) 7.20 (2H), 7.02(1H),4.99 (2H,N-CH2-N), 2.45(4H, N-CH2), 2.32 (-CH3), 2.26 (CH3), 1.55 (m, 4H) and 1.42 (m, 2H) : IR υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 398.5[M+]

2-(4-bromophenyl)-5,6-dimethyl-1-[(piperazin-4-yl)methyl]-1H-benzimidazole (2fc): Yellow solid,δH ($CDCl_3$) 7.69 (2H,=CH), 7.48 (1H) 7.20 (2H), 7.02(1H),4.99 (2H,N-CH2-N), 2.72 (m, 4H , N-CH2),2.55(m, 4H, N-CH2), 2.32 (-CH3) and 2.26 (CH3): IR υmax /cm-1 (KBr) 3426, 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 400.2[M+1]

1-[2-(4-bromophenyl)-5,6-dimethyl-1H-benzimidazol-1-yl]-N,N-dimethylmethanamine (2fd): off white solid, δH ($CDCl_3$) 7.64 (m, 2H,=CH), 7.49 (m, 2H) 7.48 (s, 1H), 7.02(s, 1H),4.99 (s, 2H,N-CH2-N),2.32(m, 6H, N-CH3), 2.30 (s, 3H) and 2.26 (s, 3H) IR υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 358.6[M+]

N-{[2-(4-bromophenyl)-5,6-dimethyl-1H-benzimidazol-1-yl]methyl}-N-ethylethanamine (2fe) off white solid, δH ($CDCl_3$) 7.64 (m, 2H,=CH), 7.49 (m, 2H) 7.48 (s, 1H), 7.02(s, 1H),4.99 (s, 2H,N-CH2-N),2.32(m, 6H, N-CH3), 2.30 (s, 3H), 2.26 (s, 3H) and 1.14 (m, 6H) IR υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 386.4[M+]

2-(4-bromophenyl)-5,6-dimethyl-1-[(morpholin-4-yl)methyl]-1H-benzimidazole (2ga) Off white solid, δH ($CDCl_3$) 7.69 (2H,=CH), 7.48 (1H) 7.20 (2H), 7.02(1H),4.99 (2H,N-CH2-N), 3.66 (4H , O-CH2),2.55(4H, N-CH2), 2.32 (-CH3) and 2.26 (CH3), δC ($CDCl_3$) 163.1 (=C-F), 137.1 (=C-N), 135.14 (=C-N), 130.1(=C), 131.2, 130.7, 130.2,128.4, 121.8, 119.8,118.7,115.2, 109.2, 60.9 (N-C-N) ,51.8 (C-N) and 14.8.; υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 339.4[M+]

2-(4-bromophenyl)-5,6-dimethyl-1-[(piperidin-1-yl)methyl]-1H-benzimidazole(2gb): Light yellow solid,δH ($CDCl_3$) 7.88 (2H,=CH), 7.69 (2H) 7.30 (1H), 7.18(1H) 7.17 (2H),7.14 (1H), 6.61 (1H),4.82 (2H,N-CH2-N), 2.55 (4H,--CH2),1.65 (4H) and 1.01 (2H) , IR υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 326 (M+1.)

2-(4-bromophenyl)-5,6-dimethyl-1-[(piperazin-1-yl)methyl]-1H-benzimidazole(2gc): Dark brown color solid δH ($CDCl_3$) 7.69 (m, 3H), 7.49 (m, 2H) 7.35 (d, 1H), 7.28 (m,1H),7.17(d,1H) 4.99 (2H,N-CH2-N) 2.79 (4H, NH-CH2) and 2.52 (4H,N-CH2 IR: υmax /cm-1 (KBr) 3342 (N-H), 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 327.2 (M+1)

1-[2-(4-bromophenyl)-5,6-dimethyl-1H-benzimidazol-1-yl]-N,N-dimethylmethanamine(2gd). Yellow color solid, δH ($CDCl_3$) 7.88 (2H,=CH), 7.69 (2H) 7.28 (1H), 7.18(1H) 7.17 (2H),7.14 (1H), 6.61 (1H),4.82 (2H,N-CH2-N) 2.43 (6H, N-CH3) IR: υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 285.9[M+]

N-{[2-(4-bromophenyl)-5,6-dimethyl-1H-benzimidazol-1-yl]methyl}-N-ethylethanamine(2ge): off white solid, δH ($CDCl_3$) 7.69 (2H,=CH), 7.67 (2H) 7.28 (1H), 7.18(1H) 7.17 (2H),7.14 (1H), 6.61 (1H),4.82 (2H,N-CH2-N) 2.43 (4H, N-CH3) and 1.02 (6H) δC ($CDCl_3$) 163.1 (=C-F), 137.1 (=C-N), 135.14 (=C-N), 130.1(=C), 131.2, 130.7, 130.2,128.4, 121.8, 119.8,118.7,115.2, 109.2, 60.9 (N-C-N) ,51.8 (C-N) and 14.8.; υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 314.2[M+1]

2-(4-fluorophenyl)-5,6-dimethyl-1-[(morpholin-4-yl)methyl]-1H-benzimidazole (2ha) Off white solid, δH ($CDCl_3$) 7.69 (2H,=CH), 7.48 (1H) 7.20 (2H), 7.02(1H),4.99 (2H,N-CH2-N), 3.66 (4H , O-CH2),2.55(4H, N-CH2), 2.32 (-CH3) and 2.26 (CH3), δC ($CDCl_3$) 163.1 (=C-F), 137.1 (=C-N), 135.14 (=C-N), 130.1(=C), 131.2, 130.7, 130.2,128.4, 121.8, 119.8,118.7,115.2, 109.2, 60.9 (N-C-N) ,51.8 (C-N) and 14.8.; υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 339.4[M+]

2-(4-fluorophenyl)-5,6-dimethyl-1-[(piperidin-1-yl)methyl]-1H-benzimidazole(2hb): Light yellow solid,δH ($CDCl_3$) 7.88 (2H,=CH), 7.69 (2H) 7.30 (1H), 7.18(1H) 7.17 (2H),7.14 (1H), 6.61 (1H),4.82 (2H,N-CH2-N), 2.55 (4H,--CH2),1.65 (4H) and 1.01 (2H) , IR υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 326 (M+1.)

2-(4-fluorophenyl)-5,6-dimethyl-1-[(piperazin-1-yl)methyl]-1H-benzimidazole(2hc): Dark brown color solid δH ($CDCl_3$) 7.69 (m, 3H), 7.49 (m, 2H) 7.35 (d, 1H), 7.28 (m,1H),7.17(d,1H) 4.99 (2H,N-CH2-N) 2.79 (4H, NH-CH2) and 2.52 (4H,N-CH2 IR: υmax /cm-1 (KBr) 3342 (N-H), 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 327.2 (M+1)

1-[2-(4-fluorophenyl)-5,6-dimethyl-1H-benzimidazol-1-yl]-N,N-dimethylmethanamine(2hd). Yellow color solid, δH ($CDCl_3$) 7.88 (2H,=CH), 7.69 (2H) 7.28 (1H), 7.18(1H) 7.17 (2H),7.14 (1H), 6.61 (1H),4.82 (2H,N-CH2-N) 2.43 (6H, N-CH3) IR: υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 285.9[M+]

N-{[2-(4-fluorophenyl)-5,6-dimethyl-1H-benzimidazol-1-yl]methyl}-N-ethylethanamine(2he): off white solid, δH ($CDCl_3$) 7.69 (2H,=CH), 7.67 (2H) 7.28 (1H), 7.18(1H) 7.17 (2H),7.14 (1H), 6.61 (1H),4.82 (2H,N-CH2-N) 2.43 (4H, N-CH3) and 1.02 (6H) δC ($CDCl_3$) 163.1 (=C-F), 137.1 (=C-N), 135.14 (=C-N), 130.1(=C), 131.2, 130.7, 130.2,128.4, 121.8, 119.8,118.7,115.2, 109.2, 60.9 (N-C-N) ,51.8 (C-N) and 14.8.; υmax /cm-1 (KBr) 3052 (=C-H, sp2) 2950 (-C-H), MS (EI): m/z 314.2[M+1]

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